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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1654	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/085,849	Applicant(s) Michaeli
	Examiner Michele Flood	Art Unit 1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 27, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10-19* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on February 27, 2002. Acknowledgment is made of Applicant's cancellation of Claims 1-9, and newly submitted Claims 10-19.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 10-19 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing glucose dependent insulin secretion in a pancreatic β-cell of a mouse comprising administering an effective amount of an inhibitor of phosphodiesterase 1C, namely isobutylmethylxanthine (IBMX) and 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX) to the pancreatic β-cell of a mouse, does not reasonably provide enablement for a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in any and/all mammals, the method comprising treating the pancreatic β-cell with any and/all inhibitors of phosphodiesterase 1C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, the method comprising treating the β-cell with an inhibitor of phosphodiesterase 1C; wherein the inhibitor is an isobutylmethylxanthine derivative with substitutions at positions 2 (R1) and 8 (R2); wherein R1 and R2 are independently a moiety selected from the group consisting of an alkyl (C_1 to C_3), a flouroalkyl (F_1 to F_3), a chloroalkyl (Cl_1 to Cl_3), an aryl (C_5 to C_6), a fluoroaryl (F_1 to F_2), and a chloroaryl (Cl_1 to Cl_2); wherein the inhibitor is selected from the group consisting of IBMX, zaprinast, 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX), and combinations thereof; wherein the mammal is a human; wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal; wherein the inhibitor is administered orally; and, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

While Applicant has demonstrated a method of increasing glucose dependent insulin

secretion in a pancreatic β-cell in a mouse comprising administering an effective amount of either isobutylmethylxanthine (IBMX), zaprinast and 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX) to the pancreatic β-cell of a mouse, Applicant has not demonstrated a method of increasing glucose dependent insulin secretion in a pancreatic β-cell, the method comprising treating the pancreatic β-cell with any and/all inhibitors of phosphodiesterase 1C, wherein the method of treatment comprises the oral administration of the claim-designated compositions to any and all mammals, and wherein the mammal is human, as broadly claimed. On page 32, lines 8-16, the Office notes that while Applicant describes the injection of PDE inhibitors into various strains of mice in "Example 3", nowhere in the instant application does Applicant disclose the oral administration of the claim-designated compositions to either mammals or humans. With regard to an *in vivo* method of treatment, on page 38, lines 14-18, Applicant merely mentions: "*In vivo*, elevations in intracellular calcium induced by glucose, as well as increased responsiveness to calcium/calmodulin, simultaneously increase PDE1C activity upon exposure of cells to glucose." Moreover, it should be noted that the state of the art at the time of filing suggests that the administration of the claim designated compositions to humans does not teach the claimed beneficial effect of insulin secretion, as readily by Applicant in the instant application.

Inventions targeted for insulin secretion/diabetes therapy bear a responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. Moreover, effective treatments for treating such disease conditions are relatively complicated, and may be unbelievable in the absence of supporting evidence. Claims drawn to

methods intended for the administration of compounds to mammalian pancreatic β-cells, especially wherein the mammal is human, for increasing glucose dependent insulin secretion in the pancreatic β-cells in the mammal, generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the therapeutic effective amounts of the claim-designated compositions to a human. There is no guidance in the specification, other than the demonstrated method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mouse, the method comprising treating the β-cell in a mouse with the aforementioned claim-designated compositions to the pancreatic.

Given the insufficient guidance in the specification as to how to carry out the instantly claimed invention for the proposed method of therapeutic treatment, the lack of working examples, and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel

aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

According, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed phosphodiesterase 1C would have the claimed functional effect for increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, the method comprising treating the β-cell with any and all inhibitors of phosphodiesterase 1C in any and all mammals, other than the demonstrated method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mouse with the aforementioned claim-designated inhibitors of phosphodiesterase 1C.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of Claim 10, as drafted in full, are rendered uncertain because it is unclear as to what Applicant intends to direct the subject matter of the claimed invention. For instance, while Applicant claims a "method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal", the Office notes that the claimed method comprises treating the

β-cell with an inhibitor of phosphodiesterase 1C versus treating the β-cell comprising administering the inhibitor of phosphodiesterase 1C to the mammal. Thus, it is unclear as to whether the subject matter of the claimed invention encompasses an *in vivo* method of treatment or an *ex vivo* method of treatment (e.g., for use in cell replacement therapy). The lack of clarity renders the claim ambiguous.

Claim 11 recites the limitation "derivative". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a chemical compound may be closely patterned after the subject chemical compound or may be loosely patterned after the subject chemical compound, such that it may bear no resemblance or form recognizable as the subject chemical compound which maybe chemically and/or biologically unrelated in function or form to the subject chemical compound. Applicant may overcome the rejection by replacing "derivative" with an active derivative thereof, wherein the active derivative has the same activity of said compound X.

Claim 13, line 2, recites the abbreviation "IBMX". Abbreviations in the first instance of claims should be expanded upon with the abbreviation indicated in parentheses. The abbreviations can be used thereafter. Applicant may overcome the rejection by adding IBMX after "isobutylmethylxanthine in line 1 of Claim 11.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10-14 and 18 are rejected under 35 U.S.C. 102(b) as being by anticipated Greenwald (D).

Applicant claims a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, the method comprising treating the β-cell with an inhibitor of phosphodiesterase 1C. Applicant further claims the method of claim 10, wherein the inhibitor is an isobutylmethylxanthine derivative with substitutions at positions 2 (R1) and 8 (R2). Applicant further claims the method of claim 11, wherein R1 and R2 are independently a moiety selected from the group consisting of an alkyl (C_1 to C_3), a flouroalkyl (F_1 to F_3), a chloroalkyl (Cl_1 to Cl_3), an aryl (C_5 to C_6), a fluoroaryl (F_1 to F_2), and a chloroaryl (Cl_1 to Cl_2). Applicant further claims the method of claim 10, wherein the inhibitor is selected from the group consisting of IBMX, zaprinast, 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX), and combinations thereof. Applicant further claims the method of claim 13, wherein the inhibitor is zaprinast. Applicant further claims the method of claim 10, wherein the inhibitor is administered orally.

Greenwald teaches a method comprising the oral administration of zaprinast to a mammal. Greenwald does not teach his method as a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal. However, the instantly claimed process is a one-step process of treating a pancreatic β-cell in a mammal comprising treating the β-cell with an inhibitor of phosphodiesterase 1C, wherein the inhibitor is zaprinast. Thus, the functional effect of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal is inherent to the method of using the zaprinast composition taught by Greenwald.

The reference anticipates the claimed subject matter.

Claims 10-13, 15, 16 and 18 are rejected under 35 U.S.C. 102(b) as being by anticipated Truss et al. (N).

Applicant's claimed invention was set forth above. Applicant further claims a method of claim 13, wherein the inhibitor is 8-methoxymethyl-1-methyl-3-(2-methylpropyl)xanthine (8MM-IBMX).

Truss teaches the oral administration of the claim-designated composition to a mammal. Truss does not teach his method as a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal. However, the instantly claimed process is a one-step process of treating a pancreatic β-cell in a mammal comprising treating the β-cell with an inhibitor of phosphodiesterase 1C, wherein the inhibitor is (8MM-IBMX). Thus, the functional effect of

increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal is inherent to the method of using the 8-methoxymethyl) isobutylmethylxanthine composition taught by Truss.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 10-13 and 17-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Kohnert et al. (U) in view of Weiner et al. (C), Bhagwart et al. (B) and Bosies et al. (A).

Applicant's claimed invention of Claims 10-13, and 16 was set forth above. Applicant further claims the method of claim 10, wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal. Applicant further claims the method of claim 10, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide.

Kohnert teaches a method of increasing glucose dependent insulin secretion in neonatal rat pancreatic beta-cells comprising treating the beta-cells with the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX). See Figure 3.

The teachings of Kohnert are set forth above. Kohnert does not teach a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal; wherein the inhibitor is administered orally; and, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the phosphodiesterase inhibitor taught by Kohnert in a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a rat comprising treating the pancreatic in a β-cell in the rat with the referenced inhibitor of phosphodiesterase 1C because Kohnert teaches the beneficial functional effect of the claim-designated ingredient on the secretion of insulin in a neonatal rat pancreatic β-cell assay. One of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of increasing glucose insulin secretion in a pancreatic β-cell taught by Kohnert by administering the referenced IBMX to a rat because, at the time the invention was made the use of a rodent β-cell assay as a test for the determination of rodent drug therapy was well-documented and widely accepted. Moreover, Kohnert clearly teaches that "monolayer cultures of neonatal B-cells can be readily produced by IBMX and maintained in a functional state, as defined by their secretory and biosynthetic response", and suggests that such model systems can be useful in understanding the pathogenesis of diabetic conditions.

With regard to Claim 19 wherein Applicant claims a method wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the modified method taught by Kohnert set forth immediately above because at the time the invention was made the administration of insulin, sulfonylurea and biguanide as anti-diabetic agents was well known in the art, as evidenced by the teachings of Weiner, Bhagwart and Bosies. Firstly, Weiner teaches a method of treating diabetes comprising the oral administration of an analog of insulin to a mammal. Secondly, Bhagwart teaches a method of treating diabetes comprising orally administering a therapeutic effective amount of a sulfonylurea in a sustained release dosage. Thirdly, Bosies teaches a biguanide composition which is suitable for oral administration in the treatment of diabetes. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method of increasing insulin secretion by treating a pancreatic β-cell with the inhibitor of phosphodiesterase 1C taught by the modified method of treatment taught by Kohnert to provide the claimed invention because in the patent claims, Weiner teaches that the oral administration of the insulin analog of his method is useful in treating diabetes, suppressing autoimmune response against pancreatic beta cells and maintaining at least partial pancreatic beta cell function in a mammal without causing a decrease in blood sugar level in a mammal; and, thus, the regulation of blood sugar levels in a mammal; in Column 4, lines 27-40, Bhagwart teaches that the referenced

controlled release sulfonylurea is suitable for once-a-day or 24 hour administration, is economical and convenient for the treatment of diabetes; and, in the abstract, Bosies teaches that treatment of diabetes mellitus with the referenced anti-diabetic biguanide composition lacks the typical side effects of biguanide treatment, *viz.*, lactacidosis.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed methods because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, at the time the invention was one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add any of the claimed ingredients taught by either Weiner, Bhagwart or Bosies to the modified method of increasing insulin secretion in a pancreatic β-cell in a rat taught by Kohnert to provide the claimed method because the claimed invention is no more than the combining of well known ingredients used in well known methods for increasing insulin secretion in a pancreatic β-cell in a mammal.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. The examiner can normally be reached on Monday through Friday from 7:15 am to 3:45 pm. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Brenda Brumback whose telephone number is (703) 306-3220.

MCF

August 4, 2003

Michele C. Flood

MICHELE FLOOD
PATENT EXAMINER